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# Urinary concentrations of polycyclic aromatic hydrocarbons in Israeli adults: Demographic and life-style predictors

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ABSTRACT

Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous environmental pollutants associated with adverse health outcomes, including cancer, asthma, and reduced fertility. Because data on exposure to these contaminants in Israel and the Middle East are very limited this study was conducted to measure urinary levels of PAHs in the general adult population in Israel and to identify demographic and life-style predictors of exposure.

We measured concentrations of five PAH metabolites: 1-hydroxypyrene (1OH_pyrene) and four different hydroxyphenanthrenes (1-hydroxyphenanthrene, 2-hydroxyphenanthrene, 3-hydroxyphenanthrene, 4-hydroxyphenanthrene), as well as cotinine in urine samples collected from 243 Israeli adults from the general population. We interviewed participants using structured questionnaires to collect detailed demographic, smoking and dietary data. For over 99% of the study participants, urinary concentration of at least one of the PAHs was above both the limit of detection (LOD) and the limit of quantification (LOQ). All PAHs were significantly correlated (rho = 0.67–0.92). Urinary concentration of hydroxyphenanthrenes, but not 1OH_pyrene, was significantly higher among Arabs and Druze study participants ($N = 56$) compared to Jewish participants ($N = 183$). For 4-hydroxyphenanthrene, concentration in Arabs and Druze was 1.95 (95% CI 1.50–2.52) that of Jews, after controlling for creatinine, age and cotinine levels. Urinary concentrations of all PAHs were significantly higher among current smokers or participants with higher cotinine levels and increased significantly with smoking frequency. While PAHs concentrations were not associated with cotinine concentrations in nonsmokers in the overall study population, PAHs concentration was significantly higher among nonsmoking Jews with cotinine ≥LOQ (1 μg/L), which represents exposure to environmental tobacco smoking, compared to nonsmoking Jews with cotinine concentrations <LOQ, with the highest ratio for 1OH_pyrene (*Ratio* = 2.38, 95% CI 1.47–3.85). Among nonsmoking Arabs and Druze, higher hydroxyphenanthrenes concentrations were found for those consuming grilled food once a month or more. For 3-hydroxyphenanthrene, concentration in those consuming grilled food once a month or more was 2.72 (95% CI 1.01–4.98) times that of those consuming grilled food less than once a month or not at all, after controlling for creatinine, age and cotinine levels.

In conclusion, we found that the general adult population in Israel is widely exposed to PAHs. Exposure differed by ethnic sub-groups both in magnitude and sources of exposure. The finding of higher exposure among Arabs and Druze highlights disparities in environmental exposures across subpopulations and suggests that further research and preventive measure are warranted to reduce PAHs exposure and associated health outcomes, especially in the Arab population in the Middle East.



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## Introduction

Polycyclic aromatic hydrocarbons (PAHs) are a group of over 100 chemicals that are generated during incomplete combustion of organic material, such as in coal-fired power plants and residential heating (Boström et al., 2002). PAHs are ubiquitous persistent but non bioaccumulative compounds (Bergman et al., 2013). These substances generally are found in the environment as complex mixtures rather than as single compounds. In the general population, exposure to PAHs can potentially occur via numerous exposure pathways, including active and secondhand smoking (also called environmental tobacco smoke), exposure in indoor and ambient air, and consumption of grilled and smoked foods (CDC, 2013; Phillips, 1999; Suwan-ampai et al., 2009).

Several adverse health outcomes in humans were found to be associated with exposure to PAHs. Evidence indicates that exposure to PAHs may result in reproductive, developmental, hematologic, cardiovascular, neurologic, and immunologic toxicities as well as cancer (Straif et al., 2005). In parallel, new evidence is gathering regarding other harmful effects. For example, a recent study found high prenatal PAHs exposure to be associated with symptoms of anxiety/depression and attention problems (Perera et al., 2012).

Exposure to PAHs is not generally monitored in human biomonitoring surveys, so data on magnitude and predictors of PAHs exposure of the general population are limited, mostly available from the US (CDC, 2013) and Germany (Schulz et al., 2007). 1-Hydroxypyrene (1OH_pyrene) is widely considered as an appropriate biomarker for exposures to PAHs on the basis that pyrene is rapidly distributed, metabolized and eliminated from the body (Aquilina et al., 2010).

Over the last decades, Israel, located in the Middle-East region, has undergone a transition from a developing country into a modern life-style, industrial state with a unique multi-ethnic and multi-cultural society. While ~80% of Israelis are Jews, there is a large minority of Israeli Arabs and Druze who are distinct by cultural, socio-demographic and life-style factors, with higher rates living in rural areas.

The goal of the current study was to measure urinary levels of various PAHs in the general adult population in Israel and to determine the demographic, smoking and dietary predictors of exposure, in order to support evidence based public health policy.

## Materials and methods

### *Study design, settings and participants*

The current study is based on the Israeli Biomonitoring Study which was a cross-sectional study on exposure of Israeli adults from the general population to environmental chemicals and/or their metabolites, measured in urine samples. The primary objective of the biomonitoring study was to provide information on exposure to environmental chemicals in Israel in order to support public health policy. Aims and methods of the biomonitoring study are further detailed in our previous publications (Berman et al., 2013a,b).

The eligible population included Israeli adults, aged 20–74, aiming to represent the Israeli non-institutionalized adult population. Recruitment, interviewing and sampling took place between February and June 2011. The potential sample size was 300 individuals, assuming up to 20% of missing data, incomplete questionnaires and invalid urine samples, to reach a planned sample size of 250 individuals. The parameters for defining the sample were selected so as to represent the population distribution of urban versus rural dwelling (with urban defined as population more than 2000) and the two major ethnic groups in Israel (Jews and Arabs) as well as wide geographical representation. Overall, 20 cities/towns were selected, with 4 within the Arab sector (3 urban, 1 rural) and 16 within the Jewish sector (15 urban, 1 rural), representing the relative proportion of the ethnic groups in Israel. In each city/town, interviewers were requested to interview 15 people. Within each city/town, interviewers were required to select 5 separate areas. Within each area, recruitment was done by "knocking on doors" and interviewing those who met the inclusion criteria and agreed to participate, including providing a urine sample. The inclusion criteria were age (20–74) and ability to answer the questionnaire in Hebrew or Arabic. The response rate was 29%, excluding individuals not eligible for the study and individuals not at home at the time of the visit. People refusing participation were replaced by "knocking on the next door". Participants were not targeted for specific health status and were not included or excluded on the basis of their potential for low or high exposures to environmental chemicals including tobacco exposure. Of 249 participants eventually included in the biomonitoring study, 243 were examined for PAHs urinary levels.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Sheba Tel Hashomer Helsinki Committee. Written informed consent was obtained for all respondents. Participation in the study was voluntary. At the time of recruitment participants received a note explaining that they would receive individual results on urinary concentrations of environmental contaminants if they requested them during their interview or if their individual urinary metabolite results were unusual (more than 10 times the 90th percentile for the study population). All individuals receiving results were invited to contact the study coordinator for additional information. All analysis of data for the study was conducted without details on the identity of the participants.

### *Data sources and variables*

Study participants were interviewed using a structured questionnaire. The interviews were administered by trained interviewers. The interview consisted of a health and lifestyle questionnaire, including smoking habits, demographic questionnaire, a 24 h dietary recall and a food frequency questionnaire. All completed questionnaires were returned to the Israel Center for Disease Control for data entry, quality assurance and analysis. Socio-demographic and personal variables included age (analyzed as a continuous variable, and also grouped as "younger", 20–44 years, and "older" 45–74 years), sex (males/females), ethnicity (Jews/Arabs and Druze), urbanicity (urban/rural), country of birth (Israel/other), education (lower education [below high school qualification]/high school education and above), marital status (single/married/divorce/widowed) and average monthly household income in shekels (<5000/5000–10,000/>10,000).

Dietary questions included vegetarian status, grilled food consumption and smoked food consumption. Questions used were: "Do you define yourself as vegetarian or vegan?", "How frequently do you eat food that was cooked on a grill or over open fire?", "How frequently do you eat smoked products, e.g. sausage, fish or smoked cheese?". Based on the first question, vegetarian status was classified as vegetarian, vegan or not-vegetarian. Based on the second and third question, participants were classified by grilled or smoked food consumption (No or less than once per month vs. Yes, for each).

Smoking status was based on self-report, validated by our previous report on cotinine levels (Levine et al., 2013). Questions used for active tobacco smoking status were: "Do you currently smoke, including hookah (water pipe)?", "What do you currently smoke, or what did you smoke before? (cigarettes, cigars, pipe, waterpipe, other)", "How many cigarettes do you smoke per day or per week?" Based on the first question, participants were classified as tobacco smokers (of any kind) or nonsmokers. Active smoking variables were smoking type (cigarettes/waterpipe only) and cigarette

smoking frequency (<10 cigarettes/day, 10–20 cigarettes/day, >20 cigarettes/day). Some of the participants categorized as cigarette smokers also smoked cigars or were waterpipe smokers.

Urine spot samples were collected in 120-mL urine specimen containers. All urine samples were maintained at below 4 °C for a maximum of 24 h until they were transported to the Sheba Medical Center at Tel Hashomer. Urine samples were aliquoted at Sheba Medical Center and frozen at −20 °C. Within four months of collection, urine samples were shipped to the University of Erlangen—Nuremberg in Germany on dry ice (−70 °C), where they were analyzed.

Laboratory analyzes of PAHs, cotinine and creatinine were performed at the Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine, University Erlangen-Nuremberg in Germany using the following methods. The determination of hydroxylated PAHs (1-hydroxypyrene (1OH_pyrene), 1-hydroxyphenanthrene (1OH_phen), sum of 2- and 9-hydroxyphenanthrene (2OH_phen), 3-hydroxyphenanthrene (3OH_phen), 4-hydroxyphenanthrene (4OH_phen) was performed using high-performance liquid chromatography with fluorescence detection (HPLC-FD) (Hemat et al., 2012). Clean-up took place using an online extraction procedure with a copper phthalocyanine-modified silica gel phase (pre concentration column). Calibration standards were prepared by spiking pooled non-smoker urine with the hydroxylated PAHs. The limits of quantification (LOQ) were 16 ng/L urine for 1OH_phen, 4 ng/L for 2OH_phen, 5 ng/L for 3OH_phen, 8 ng/L for 4OH_phen and 12 ng/L for 1OH_pyrene (Feldt et al., 2014). Aliquots of quality control material prepared in human urine were analyzed in each series to verify the comparability of the analyses. Analytical accuracy was demonstrated for 1OH_pyrene (as well as cotinine) by the successful participation in the proficiency test of the German External Quality Assessment Scheme (G-EQUAS) (Göen et al., 2012).

Cotinine in urine was determined using a gas chromatography mass spectrometry procedure validated and published by the working group "Analyzes in biological materials" (Müller, 2003). In brief, cotinine was extracted from the urine using dichloromethane and quantified after gas chromatographic separation by mass spectrometry in single ion monitoring mode (Eckert et al., 2011), as further detailed in our previous report on cotinine levels (Levine et al., 2013). LOQ was 1 μg/L for cotinine. Limit of detection (LOD) and LOQ were calculated based on a signal-to-noise ratio of 1 to 3 and 1 to 6, respectively. Urinary analyte concentrations were provided in units of μg/L. These concentrations were divided by urinary creatinine concentrations (g creatinine/L urine) to generate creatinine-adjusted analyte concentrations. Creatinine in urine was determined photometrically as picrate according to the Jaffé method (Larsen, 1972).

### *Statistical methods*

We calculated medians, geometric means, 95% confidence intervals and maximum values for urinary analyte concentrations and for creatinine-adjusted analytes for each of the PAHs metabolites. Concentrations below the limit of quantification (LOQ) for an analyte were replaced by the limit of detection (LOD) for that analyte, and concentrations below the LOD were replaced with the LOD divided by the square root of 2 (Hornung and Reed, 1990).

The main outcome variable was geometric mean (GM) of PAHs concentration. We also reported the proportion ≥LOQ. Associations between continuous variables such as PAHs metabolites and cotinine were assessed using Spearman correlation tests, overall, and stratified by ethnicity.

As a part of a univariate analysis we compared geometric means of urinary PAH metabolites not adjusted to creatinine of demographic, dietary and smoking subgroups using a ratio t-test procedure on a lognormal distribution. Analysis of smoking subgroups included smoking habits among smokers and cotinine levels by a cut-off ≥4 μg/L (for overall analysis) and ≥1 μg/L (for nonsmokers subgroup analysis) representing higher active and/or passive tobacco exposure (Heinrich et al., 2005). Differences between subgroups were also assessed based on ratios obtained from univariate linear regression, with subgroup indicator as an independent factor and log-transformed PAHs as a dependent variable. We further applied an antilog function to a linear effect of factors examined, resulting in a multiplicative effect (ratio). A multivariable analysis was performed in a similar way to analyze differences by ethnicity, controlling for significant predictors for at least one PAH, which were creatinine, cotinine and age as continuous variables. Similar analyses were used for subgroup analyses, stratified by ethnicity and by smoking status. $p$ Value <0.05 was considered statistically significant. We used SAS 9.2 for all the analyses.

## Results

### *Characteristics of the study population*

The 243 study participants (51% males) were composed of 183 (77%) Jews, 56 (23%) Arabs and Druze and 4 with other ethnicity (Table 1). 66% of the study population was aged 20–44 years (Mean age = 38.5, SD = 12.6). Participants in the study came from five geographic regions in Israel: Northern ($N$ = 15), Haifa ($N$ = 69), Central ($N$ = 49), Tel Aviv ($N$ = 60), and Southern ($N$ = 50).

### *Urinary concentrations of PAHs metabolites*

Urinary PAHs were detected at levels >LOQ for over 90% of study participants for all metabolites, except 4OH-phen (63%), which was present at the lowest concentrations (Table 2). 1OH_phen and 1OH_pyrene were the PAHs metabolites present at the highest concentrations, followed by 3OH_phen and 2OH_phen. All metabolites (including 1OH_pyrene and each of the hydroxyphenanthrenes) were significantly correlated with each other (rho = 0.67–0.92, $p$ < 0.001; strongest for 2OH_phen and 3OH_phen; rho = 0.92) (Table 3). After stratification for ethnicity, correlations of PAHs were remarkably similar for Jews or Arabs and Druze (data not shown).

### *Demographic and dietary predictors*

Urinary concentrations of 1OH_phen, 2OH_phen and 4OH_phen were significantly higher among Arabs and Druze compared to Jews (Table 1). Levels of all PAHs metabolites tended to be higher for 20–44 years age group compared to 45–74 years, but reached statistical significance only for 1OH_pyrene (GM = 198 ng/L vs. 130 ng/L; $p$ = 0.008). Urinary concentrations of all hydroxyphenanthrenes, but not 1OH_pyrene, were significantly higher among those residing in rural compared to urban areas. In the univariate analysis, no significant differences for any of the PAHs were found by gender, body mass index, educational level, country of birth, marital status, household income or dietary habits (grilled food consumption, smoked food consumption, vegetarian status).

In a multivariable model, adjusted for cotinine, creatinine and age (Table 4), all urinary hydroxyphenanthrenes but not 1OH_pyrene were significantly higher among Arabs and Druze compared to Jews, most notably for 1OH_phen (ratio = 1.87; 95% CI 1.44–2.42; $p$ < 0.001) and 4OH_phen (ratio = 1.95; 95% CI 1.50–2.52; $p$ < 0.001). Of note, associations were accentuated after adjustment, especially for cotinine. Results were materially unchanged (data not shown) after adjustment for other variables such as gender or body mass index.

**Table 1**
Participants' characteristics and PAHs urinary concentrations geometric mean (ng/L), Israeli adults, 2011 ($N = 243$).

| Characteristics[a] | % ($n/N$) | 1OH_pyrene | | | 1OH_phen | | | 2OH_phen[b] | | | 3OH_phen | | | 4OH_phen[c] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | GM | 95% CI | $p$-Value | GM | 95% CI | $p$-Value | GM | 95% CI | $p$-Value | GM | 95% CI | $p$-Value | GM | 95% CI | $p$-Value |
| Sex | | | | | | | | | | | | | | | | |
| Male | 51.4 (125/243) | 186 | 152;228 | 0.269 | 184 | 151;224 | 0.647 | 98 | 83;116 | 0.373 | 144 | 117;177 | 0.164 | 28 | 23;35 | 0.832 |
| Female | 48.6 (118/243) | 157 | 127;196 | | 197 | 159;245 | | 88 | 74;104 | | 118 | 96;144 | | 29 | 24;36 | |
| Age, years | | | | | | | | | | | | | | | | |
| 20–44 | 65.8 (160/243) | 198 | 167;235 | 0.008 | 210 | 178;249 | 0.059 | 100 | 86;115 | 0.097 | 143 | 119;170 | 0.095 | 30 | 25;36 | 0.483 |
| 45–74 | 34.2 (83/243) | 130 | 98;172 | | 157 | 119;206 | | 81 | 65;100 | | 110 | 86;141 | | 27 | 23;34 | |
| BMI | | | | | | | | | | | | | | | | |
| <25 | 58.3 (129/221) | 186 | 153;227 | 0.087 | 190 | 157;230 | 0.618 | 90 | 76;107 | 0.876 | 133 | 109;162 | 0.538 | 28 | 23;34 | 0.828 |
| ≥25 | 41.7 (92/221) | 141 | 108;184 | | 176 | 136;227 | | 92 | 76;112 | | 121 | 94;155 | | 29 | 23;37 | |
| Ethnicity | | | | | | | | | | | | | | | | |
| Jews | 76.6 (183/239) | 171 | 143;204 | 0.972 | 168 | 142;200 | 0.004 | 84 | 73;97 | 0.005 | 124 | 104;146 | 0.227 | 27 | 25;36 | 0.004 |
| Arabs and Druze | 23.4 (56/239) | 170 | 127;228 | | 277 | 214;360 | | 127 | 102;157 | | 153 | 114;204 | | 43 | 23;34 | |
| Residence | | | | | | | | | | | | | | | | |
| Urban | 88.1 (214/243) | 168 | 144;198 | 0.497 | 178 | 152;207 | 0.011 | 87 | 76;99 | 0.003 | 120 | 103;140 | 0.002 | 27 | 23;31 | 0.003 |
| Rural | 11.9 (29/243) | 197 | 128;305 | | 316 | 209;477 | | 152 | 113;206 | | 241 | 168;346 | | 52 | 33;83 | |
| Education level | | | | | | | | | | | | | | | | |
| Lower education | 21.3 (51/239) | 151 | 105;216 | 0.320 | 183 | 124;268 | 0.742 | 92 | 68;125 | 0.923 | 125 | 84;186 | 0.700 | 32 | 23;45 | 0.506 |
| High school and above | 78.7 (188/239) | 181 | 154;214 | | 194 | 165;227 | | 94 | 82;107 | | 134 | 115;156 | | 28 | 24;33 | |
| Grilled food consumption | | | | | | | | | | | | | | | | |
| No or <1/month | 69.0 (167/242) | 177 | 147;213 | 0.513 | 193 | 162;230 | 0.731 | 93 | 28;314 | 0.897 | 134 | 112;160 | 0.581 | 30 | 25;36 | 0.441 |
| ≥1/month | 31.0 (75/242) | 159 | 124;205 | | 183 | 140;239 | | 92 | 74;114 | | 123 | 95;159 | | 27 | 20;35 | |
| Smoked food consumption | | | | | | | | | | | | | | | | |
| No or < 1/month | 74.5 (178/239) | 171 | 143;205 | 0.933 | 187 | 157;224 | 0.693 | 91 | 78;106 | 0.479 | 130 | 109;154 | 0.781 | 28 | 24;34 | 0.554 |
| ≥1/month | 25.5 (61/239) | 174 | 131;231 | | 200 | 155;224 | | 101 | 82;123 | | 136 | 103;179 | | 31 | 23;42 | |
| Vegetarian status | | | | | | | | | | | | | | | | |
| Vegetarian | 2.9 (7/239) | 84 | 21;333 | Ref. | 105 | 28;399 | Ref. | 51 | 25;104 | Ref. | 93 | 42;207 | Ref. | 17 | 7;45 | Ref. |
| Vegan | 4.6 (11/239) | 175 | 80;382 | 0.202 | 226 | 111;461 | 0.167 | 106 | 63;178 | 0.112 | 117 | 47;291 | 0.682 | 45 | 22;92 | 0.083 |
| Non-vegetarian | 92.5 (221/239) | 176 | 151;206 | 0.104 | 195 | 168;227 | 0.161 | 94 | 82;106 | 0.098 | 132 | 114;154 | 0.427 | 29 | 25;34 | 0.233 |

[a] There were no significant differences by country of birth, household income or marital status.
[b] 2OH_phen is the sum of 2- and 9-hydroxyphenanthrene.
[c] $N = 241$ for 4OH_phen due to 2 missing.

**Table 2**
PAHs metabolites concentrations in urine (ng/Liter and ng/g creatinine), Israeli adults, 2011(N = 243).

| Metabolite | LOQ (ng/L) | % >LOQ | Unadjusted (ng/L) | | | | | Creatinine adjusted (ng/g) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Median | Maximum | Geometric mean | Lower 95% CI | Upper 95% CI | Median | Geometric mean | Lower 95% CI | Upper 95% CI |
| 1OH_pyrene | 12 | 91 | 204.20 | 2690.42 | 171.64 | 147.94 | 199.15 | 144.51 | 137.07 | 122.80 | 153.91 |
| 1OH_phen | 16 | 90 | 218.84 | 2584.57 | 190.35 | 164.66 | 220.05 | 149.05 | 152.02 | 135.21 | 170.91 |
| 2OH_phen[a] | 4 | 99 | 94.75 | 1050.10 | 92.91 | 82.42 | 104.72 | 69.83 | 74.19 | 67.22 | 81.89 |
| 3OH_phen | 5 | 97 | 140.65 | 1887.11 | 130.56 | 113.10 | 150.73 | 92.67 | 104.27 | 92.81 | 117.14 |
| 4OH_phen[b] | 8 | 63 | 31.92 | 358.56 | 28.92 | 25.07 | 33.37 | 23.52 | 23.13 | 20.20 | 26.48 |

[a] 2OH_phen is the sum of 2- and 9-hydroxyphenanthrene.
[b] N = 241 for 4OH_phen due to 2 missing.

**Table 3**
Spearman correlation coefficients between PAHs metabolites and cotinine (unadjusted to creatinine)[a], Israeli adults, 2011(*N* = 243).

| | 1OH_pyrene | 1OH_phen | 2OH_phen[b] | 3OH_phen | 4OH_phen | Cotinine | Cotinine (Jews) | Cotinine (Arabs and Druze) |
|---|---|---|---|---|---|---|---|---|
| 1OH_pyrene | 1.000 | 0.834 | 0.786 | 0.836 | 0.669 | 0.386 | 0.443 | 0.196 |
| 1OH_phen | | 1.000 | 0.900 | 0.896 | 0.835 | 0.380 | 0.481 | 0.147 |
| 2OH_phen[b] | | | 1.000 | 0.923 | 0.850 | 0.399 | 0.499 | 0.179 |
| 3OH_phen | | | | 1.000 | 0.804 | 0.484 | 0.556 | 0.308 |
| 4OH_phen | | | | | 1.000 | 0.402 | 0.496 | 0.225 |

[a] *p*-Value for all correlations coefficients were <0.001, except for correlations between PAHs and cotinine among Arabs and Druze ($n = 56$) [$p > 0.05$, except for 3OH_phen; $p = 0.02$].
[b] 2OH_phen is the sum of 2- and 9-hydroxyphenanthrene.

When urbanicity was introduced to the multivariable model, it was not significant, while ethnicity remained significant for all hydroxyphenanthrenes. In a subgroup univariate analysis, among nonsmokers Arabs and Druze, hydroxyphenanthrenes levels were significantly higher (ratios of 2.0–2.6) among those residing in rural areas (19.5%) compared to those residing in urban areas, but no such difference by urbanicity was observed among nonsmoking Jews (2.0% residing in rural areas). In a subgroup univariate analysis, consumption of grilled food once a month or more often was a common (75.6% of the population) and significant risk factor for higher 1OH_phen, 2OH_phen and 3OH_phen levels among nonsmoking Arabs and Druze ($N = 41$) but not among nonsmoking Jews (64.7% consumed grilled food once a month or more often). This finding was most notable for 3OH_phen (ratio = 2.87; 95% CI 1.37–6.02, $p = 0.008$), slightly weakened after adjustment for cotinine, creatinine and age as continuous variables (ratio = 2.72; 95% CI 1.01–4.98, $p = 0.05$).

*Smoking (including cotinine levels) predictors*

Cotinine was significantly correlated with any of PAHs (rho = 0.38–0.48) [Table 3]. However, correlations between cotinine and PAHs were stronger and significant for Jews (rho = 0.44–0.56), while weaker and non-significant (rho = 0.15–0.23, except for 3OH_phen; rho = 0.31, $p = 0.02$) for Arabs and Druze. Urinary concentrations of all PAHs were significantly higher for current smokers compared to non-smokers as categorized based on self-reporting, as well as by cotinine urinary concentrations (Table 5). Among the group of waterpipe only smokers ($N = 13$), 1OH_pyrene levels were relatively high (GM = 205 ng/L vs. GM = 135 ng/L among nonsmokers) and not significantly different from cigarette smokers (GM = 233 ng/L), while hydroxyphenanthrenes levels among waterpipe smokers were similar to nonsmokers. For all PAHs, concentrations increased monotonically with increasing number of cigarettes smoked per day (GM = 429 ng/L for 1OH_phen among smokers >20 cigarettes/day) with stronger associations observed for hydroxyphenanthrenes than for 1OH_pyrene.

After stratification for ethnicity (Tables 6a and 6b), differences in PAHs by cotinine levels were stronger for Jews (GM doubled or more for participants with higher cotinine levels) than for Arabs and Druze (GM 1.2–1.6 times higher for participants with higher cotinine levels). Among Jews, urinary concentrations of all PAHs were significantly higher for current smokers compared to non-smokers (GM 1.7–2.0 times higher). Monotonic increase in PAHs concentrations by number of cigarettes smoked per day was observed for Jews, while for Arabs and Druze, concentration did not increase for the five smokers >20 cigarettes/day (for example, for 1OH_pyrene, GM = 403 ng/L for 10–20 cigarettes/day compared to GM = 253 ng/L for >20 cigarettes/day). PAHs levels were significantly higher (except 4OH_phen) among nonsmoking Jews with cotinine concentrations ≥LOQ (1 μg/L), with highest ratio for 1OH_pyrene ($R = 2.38$, 95% CI 1.47–3.85; $p = 0.001$). In contrast, PAHs levels did not differ by cotinine levels among nonsmoking Arabs and Druze.

## Discussion

This study, the first human biomonitoring study of PAHs exposure among general adult population in the Middle East region, shows that the general population in Israel is widely exposed to polycyclic aromatic hydrocarbons. Individual PAH metabolites were highly correlated among each other, suggesting common sources of exposure and similar metabolic pathways (Li et al., 2008). PAHs were associated with cotinine levels and with smoking habits, including smoking frequency. Levels of hydroxyphenanthrenes, but not 1OH_pyrene, were significantly higher among the Arabs and Druze study participants compared to the Jewish population, after controlling for creatinine, age and cotinine levels. These populations differed by predictors of PAHs exposure among nonsmokers (all or some metabolites): environmental tobacco smoking (as measured by cotinine levels) for Jews, grilled food consumption and rural residence for Arabs and Druze.

Geometric mean creatinine adjusted urinary concentrations of four hydroxyphenanthrenes (1OH_phen, 2OH_phen, 3OH_phen, 4OH_phen) were comparable to those found in the general US population aged 20 and older in 2007–2008 (CDC, 2013) whereas concentrations of 1OH_pyrene were higher in our study population (140 ng/g compared to 80 ng/g in the US). On the other hand, urinary concentrations of 1OH_phen, 2OH_phen and 3OH_phen were much lower in our study population compared to the general German

**Table 4**
PAHs urinary concentrations by ethnicity, Israeli adults, 2011 ($N = 243$), results of linear regression model of log-transformed PAH values, adjusted for creatinine, cotinine and age.

| Characteristics | 1OH_pyrene | | 1OH_phen | | 2OH_phen[a] | | 3OH_phen | | 4OH_phen | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *R* (95% CI)[b] | *p*-Value | *R* (95% CI) | *p*-Value | *R* (95% CI) | *p*-Value | *R* (95% CI) | *p*-Value | *R* (95% CI) | *p*-Value |
| Arabs and Druze vs. Jews—crude | 0.99 (0.69; 1.40) | 0.937 | 1.63 (1.16; 2.29) | 0.005 | 1.50 (1.13; 1.98) | 0.004 | 1.22 (0.87; 1.72) | 0.243 | 1.65 (1.18; 2.30) | 0.004 |
| Arabs and Druze vs. Jews—adjusted for creatinine | 1.02 (0.76; 1.38) | 0.874 | 1.69 (1.26; 2.26) | <0.001 | 1.54 (1.21; 1.97) | 0.002 | 1.27 (0.94; 1.70) | 0.123 | 1.69 (1.23; 2.33) | 0.002 |
| Arabs and Druze vs. Jews—adjusted for cotinine | 1.08 (0.77; 1.50) | 0.653 | 1.81 (1.81; 2.46) | <0.001 | 1.64 (1.27; 2.11) | <0.001 | 1.38 (1.02; 1.86) | 0.038 | 1.91 (1.44; 2.52) | <0.001 |
| Arabs and Druze vs. Jews—adjusted for creatinine and cotinine | 1.12 (0.86; 1.48) | 0.394 | 1.89 (1.46; 2.44) | <0.001 | 1.69 (1.37; 2.09) | <0.001 | 1.43 (1.11; 1.84) | 0.006 | 1.97 (1.52; 2.54) | <0.001 |
| Arabs and Druze vs. Jews—adjusted for creatinine, cotinine and age (years) | 1.13 (0.86; 1.49) | 0.365 | 1.87 (1.44; 2.42) | <0.001 | 1.68 (1.36; 2.08) | <0.001 | 1.43 (1.11; 1.84) | 0.006 | 1.95 (1.50; 2.52) | <0.001 |

[a] 2OH_phen is the sum of 2- and 9-hydroxyphenanthrene.
[b] Ratios (*R*) represent the multiplicative difference in PAH concentrations between Arab and Druze vs. Jewish study participants.

**Table 5**
PAHs urinary concentrations (ng/L) by smoking characteristics and cotinine levels, Israeli adults, 2011 (N = 243).

| Variable | *N* | 1OH_pyrene | | 1OH_phen | | 2OH_phen[a] | | 3OH_phen | | 4OH_phen | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | GM (95%CI) | *p*-Value | GM (95%CI) | *p*-Value | GM (95%CI) | *p*-Value | GM (95%CI) | *p*-Value | GM (95%CI) | *p*-Value |
| Cotinine levels | | | | | | | | | | | |
| <4 μg/L | 140 | 130 (106; 159) | <0.001 | 150 (123;183) | <0.001 | 73 (62; 87) | <0.001 | 94 (77; 115) | <0.001 | 22 (19;26) | <0.001 |
| ≥4 μg/L | 103 | 251 (206; 305) | | 263 (216;320) | | 128 (111; 148) | | 204 (171;244) | | 42 (34;53) | |
| Smoking status[b] | | | | | | | | | | | |
| Non-smokers | 144 | 135 (110; 163) | 0.001 | 154 (127; 186) | 0.002 | 76 (64; 89) | <0.001 | 97 (81; 118) | <0.001 | 23 (19; 27) | <0.001 |
| Current smokers | 90 | 233 (187; 289) | | 247 (197; 310) | | 119 (100; 142) | | 189 (154; 233) | | 39 (30; 50) | |
| Smoking mode (among current smokers)[c] | | | | | | | | | | | |
| Waterpipe only | 13 | 205 (122; 343) | 0.629 | 162 (110;239) | 0.034 | 79 (50;125) | 0.055 | 130 (75;225) | 0.132 | 21 (12;37) | 0.037 |
| Cigarettes | 76 | 239 (186; 308) | | 271 (209;350) | | 129 (106;157) | | 203 (162;255) | | 44 (34; 58) | |
| Number of cigarettes/day (among cigarette smokers) | | | | | | | | | | | |
| <10 | 24 | 170 (108; 268) | Ref. | 161 (95; 273) | Ref. | 86 (61; 121) | Ref. | 131 (89; 195) | Ref. | 21 (14; 34) | Ref. |
| 10–20 | 34 | 252 (167; 380) | 0.179 | 307 (207; 455) | 0.007 | 135 (98; 187) | 0.009 | 219 (150; 321) | 0.020 | 55 (36; 83) | <0.001 |
| >20 | 18 | 339 (233; 495) | 0.036 | 429 (319; 575) | <0.001 | 204 (165; 251) | <0.001 | 315 (231; 429) | 0.001 | 81 (52; 126) | <0.001 |

[a] 2OH_phen is the sum of 2- and 9-hydroxyphenanthrene.
[b] Smoking status for 5 self-reported non-smokers with creatinine-adjusted cotinine levels above 150 μg/g was set to missing. Additional 4 participants were excluded due to unverified smoking status.
[c] Data on smoking mode was missing for 1 participant.

**Table 6a**
PAHs urinary concentrations (ng/L) by smoking characteristics and cotinine levels, Israeli adults, 2011, Jews ($N = 183$).

| Variable | N | 1OH_pyrene | | 1OH_phen | | 2OH_phen[a] | | 3OH_phen | | 4OH_phen | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | GM (95%CI) | p-Value | GM (95%CI) | p-Value | GM (95%CI) | p-Value | GM (95%CI) | p-Value | GM (95%CI) | p-Value |
| Cotinine levels | | | | | | | | | | | |
| <4 μg/L | 101 | 121 (94; 155) | <0.001 | 122 (97; 154) | <0.001 | 62 (51; 76) | <0.001 | 83 (66; 105) | <0.001 | 18 (15; 22) | <0.001 |
| ≥4 μg/L | 82 | 261 (210; 325) | | 249 (198; 314) | | 123 (105; 145) | | 201 (164; 245) | | 39 (30; 51) | |
| Smoking status | | | | | | | | | | | |
| Non-smokers | 100 | 128 (100; 164) | 0.001 | 126 (100; 158) | <0.001 | 65 (53; 79) | <0.001 | 88 (70; 111) | <0.001 | 19 (16; 23) | <0.001 |
| Current smokers | 75 | 231 (179; 297) | | 227 (175; 295) | | 110 (90; 134) | | 176 (139; 223) | | 35 (27; 46) | |
| Smoking mode (among current smokers)[b] | | | | | | | | | | | |
| Waterpipe only | 10 | 236 (127; 436) | 0.958 | 160 (100; 257) | 0.094 | 73 (42; 128) | 0.106 | 123 (59; 256) | 0.234 | 16 (9; 28) | 0.021 |
| Cigarettes | 64 | 231 (174; 307) | | 245 (182; 329) | | 118 (95; 147) | | 187 (145; 242) | | 41 (30; 55) | |
| Number of cigarettes/day (among cigarette smokers) | | | | | | | | | | | |
| <10 | 22 | 171 (103; 282) | Ref. | 155 (87; 276) | Ref. | 84 (58; 122) | Ref. | 131 (85; 201) | Ref. | 21 (13; 34) | Ref. |
| 10–20 | 30 | 236 (150; 373) | 0.410 | 284 (184; 440) | 0.025 | 123 (87; 175) | 0.039 | 201 (132; 205) | 0.075 | 49 (31; 7) | <0.001 |
| >20 | 12 | 380 (222; 648) | 0.060 | 390 (258; 583) | 0.012 | 199 (153; 260) | 0.001 | 304 (212; 436) | 0.011 | 86 (55; 136) | <0.001 |
| Cotinine levels (among nonsmokers) | | | | | | | | | | | |
| <LOQ (1 μg/L) | 35 | 73 (48; 112) | 0.001 | 78 (53; 115) | 0.002 | 45 (32; 63) | 0.006 | 53 (35; 80) | 0.001 | 16 (12; 21) | 0.135 |
| ≥LOQ (1 μg/L) | 65 | 174 (131; 231) | | 163 (124; 214) | | 79 (62; 99) | | 115 (89; 150) | | 21 (16; 27) | |

[a] 2OH_phen is the sum of 2- and 9-hydroxyphenanthrene.
[b] Data on smoking mode was missing for 1 participant.

**Table 6b**
PAHs urinary concentrations (ng/L) by smoking characteristics and cotinine levels, Israeli adults, 2011, Arabs and Druze (N = 56).

| Variable | N | 1OH_pyrene | | 1OH_phen | | 2OH_phen[a] | | 3OH_phen | | 4OH_phen | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | GM (95%CI) | p-Value | GM (95%CI) | p-Value | GM (95%CI) | p-Value | GM (95%CI) | p-Value | GM (95%CI) | p-Value |
| Cotinine levels | | | | | | | | | | | |
| <4 μg/L | 36 | 152 (104; 223) | 0.322 | 259 (180; 372) | 0.486 | 118 (89; 157) | 0.375 | 128 (87; 190) | 0.108 | 38 (26; 55) | 0.268 |
| ≥4 μg/L | 20 | 207 (127; 337) | | 314 (218; 452) | | 144 (102; 205) | | 209 (137; 319) | | 54 (31; 93) | |
| Smoking status | | | | | | | | | | | |
| Non-smokers | 41 | 144 (101; 206) | 0.141 | 246 (177; 341) | 0.190 | 110 (85; 143) | 0.055 | 122 (86; 174) | 0.022 | 36 (26; 51) | 0.103 |
| Current smokers | 14 | 235 (154; 358) | | 365 (246; 541) | | 176 (125; 247) | | 261 (173; 395) | | 64 (33; 125) | |
| Smoking mode (among current smokers) | | | | | | | | | | | |
| Waterpipe only | 3 | 128 (20; 847) | 0.110 | 168 (28; 991) | 0.098 | 104 (19; 569) | 0.078 | 154 (49; 482) | 0.156 | 52 (4; 784) | 0.722 |
| Cigarettes | 11 | 276 (176; 432) | | 451 (318; 641) | | 203 (145; 284) | | 302 (186; 489) | | 69 (30; 156) | |
| Number of cigarettes/day (among cigarette smokers) | | | | | | | | | | | |
| <10 | 2 | 163 (20; 1355) | Ref. | 242 (59; 1003) | Ref. | 108 (9; 1338) | Ref. | 136 (13; 1459) | Ref. | Unavailable due to small numbers | Ref. |
| 10–20 | 4 | 403 (117; 1385) | 0.032 | 540 (243; 1199) | 0.014 | 275 (174; 435) | 0.009 | 429 (228; 807) | 0.020 | | 0.099 |
| >20 | 5 | 253 (121; 526) | 0.177 | 501 (270; 929) | 0.015 | 205 (111; 379) | 0.039 | 313 (110; 891) | 0.066 | | 0.589 |
| Cotinine levels (among nonsmokers) | | | | | | | | | | | |
| <LOQ (1 μg/L) | 20 | 134 (78; 229) | 0.692 | 256 (155; 424) | 0.801 | 117 (77; 176) | 0.653 | 114 (62; 209) | 0.714 | 40 (24; 65) | 0.591 |
| ≥LOQ (1 μg/L) | 21 | 154 (91; 261) | | 236 (148; 376) | | 104 (73; 148) | | 130 (84; 202) | | 33 (19; 56) | |

[a] 2OH_phen is the sum of 2- and 9-hydroxyphenanthrene.

population in 1998 while 1OH_pyrene levels were higher in our population (140 ng/g compared to 110 ng/g) (Becker et al., 2003).

We found that urinary hydroxyphenanthrenes but not 1OH_pyrene concentrations were significantly higher in Jewish participants relative to Arab and Druze participants. After adjustment for age, creatinine and cotinine concentrations (mainly due to the adjustment for cotinine), associations accentuated , reaching a ratio of nearly two fold for 4OH_phen and 1OH_phen. The differences in urinary concentrations of PAHs by population sub-groups in Israel may be impacted by many factors, including exposure to ambient and indoor air pollutants, dietary preferences or lifestyle behaviors not captured by our study or differences in genetic factors impacting metabolism of these compounds, such as polymorphism in acetylators genes (Al-Daghri et al., 2013; Hansen et al., 2008). The exposure to PAHs by smoking among smokers might mask other predictors; hence analysis of risk factors among nonsmokers might elucidate mechanism of exposure.

There may be differences by population sub-groups in mode of cooking or consumption of specific food items not captured by our questionnaire. Such differences are hinted by our finding that grilled food consumption was a predictor of exposure among nonsmoking Arabs and Druze but not among Jews. Practices such as burning biomass fuels such as wood on indoor open-pit stoves, which have been associated previously with high PAHs exposure (Chen et al., 2007; Hemat et al., 2012), may be more common among Arab and Druze populations in Israel. We were unable to directly explore this hypothesis, but our finding that rural residence was a risk factor for higher PAHs levels among nonsmoking Arabs and Druze, but not Jews, give indirect evidence to support this hypothesis. In contrast, higher cotinine levels, representing exposure to environmental tobacco smoking, were found in our study to be a risk factor for PAHs exposure among nonsmoking Jews but not Arabs and Druze, giving further support to differing modes of exposure by subpopulation groups. Evidence to higher exposure to PAHs among nonsmoking people exposed to environmental tobacco smoking, as manifested by higher cotinine levels, is accumulating (Aquilina et al., 2010; Polanska et al., 2014; Suwan-ampai et al., 2009). In our study such association was found for Jews but not for Arabs and Druze. This difference might be explained by other sources of exposure among nonsmoking Arabs and Druze, previously discussed such as diet, as manifested by relatively high levels of PAHs among nonsmoking Arabs and Druze with low cotinine levels. We were unable to explore other possible differences between Jews and Arabs exposure such as associations between PAHs levels in our study and exposure to ambient air pollution, distance from major roads, and distance for industrial PAHs sources.

Further study in needed to elucidate this finding and explore mechanisms of exposure to PAHs and possible impact on health among the Arab and Druze populations. Interestingly, previous analysis in our biomonitoring study revealed higher bisphenol A (BPA) exposure in the Jewish population (Berman et al., 2014), suggesting that ethnicity may be an important predictor of exposure to selected environmental contaminants in Israel. According to NHANES 1999–2002 data, household income level and to lesser extent race/ethnicity and education attainment, were significant determinants of urinary excretion of PAH metabolites (Suwan-ampai et al., 2009). There are limited data from previous studies on the associations between urinary PAHs levels and sociodemographic determinants, and no previous data among adults from the Middle East region.

Urinary excretions of all PAHs measured in the study were 1.5–2 times higher in participants reporting current smoking than in nonsmokers. In addition, cotinine levels, representing total exposure to active and voluntary and involuntary tobacco smoke, were correlated with PAHs levels (Spearman correlation 0.35–0.45). However, correlation of cotinine with PAHs was weaker for Arabs and Druze, implying that the relative contribution of tobacco smoking exposure to PAHs exposure is smaller in this group compared to Jews, i.e. another support for the hypothesis that there are additional sources of exposure, discussed before. The contribution of active cigarette smoking to PAHs exposure is well established. Multiple studies have consistently reported 1OH_pyrene concentration in urine to be 1.5–3 times higher among current smokers compared with nonsmokers, as well as for hydroxyphenanthrenes, although less frequently studied (Gündel et al., 1996; Suwan-ampai et al., 2009). Urinary PAHs levels in our study increased with number of cigarettes smoked per day. This association should not be taken for granted, as it was previously shown that the dose-response association between number of cigarettes and PAHs levels may differ between populations (Benowitz et al., 2011). Due to limited sample size we could not fully assess interaction between number of cigarettes smoked per day and PAHs levels by ethnicity, although the possibility of such difference by ethnicity was hinted by our data.

Levels of 1OH_pyrene, but not hydroxyphenanthrenes, among waterpipe only smokers were similar to cigarette smokers. This is, to the best of our knowledge, the first report of urinary levels of 1OH_pyrene among waterpipe smokers in an observational general population study. It was reported earlier that PAHs are emitted during waterpipe smoking (Shihadeh et al., 2012). This finding adds more evidence to the health risks of waterpipe smoking, to our previous findings of increased cotinine levels among exclusive waterpipe users (Levine et al., 2013) and increased utilization of health care services (Levine et al., 2012).

We found that grilled food consumption was a risk factor among nonsmoking Arabs and Druze, but we did not find associations with smoked food consumption or vegetarian status. In previous studies, differing by populations, PAHs measured and ages of participants, have found different dietary predictors of urinary PAHs levels including increased grilled fish and/or shellfish (Lee et al., 2009), consumption of grilled food and chocolate (Becker et al., 2007), consumption of grilled/boiled meat (Suwan-ampai et al., 2009). There are several possible explanations that our finding regarding dietary predictors of PAHs exposure was limited to nonsmoking Arabs and Druze. First, while our dietary questionnaire included questions on overall consumption of smoked and grilled food we did not collect detailed information on consumption of specific foods, such as fish, cheese, or meat, chocolate, and well done foods. In addition, our limited sample size might have been underpowered to show weak associations or association with rare exposures. Among smokers, PAHs exposure from smoking might have masked other weaker or more rare dietary sources. Finally, we note that differences in dietary patterns across populations may explain differences in dietary predictors. For example, consumption of smoked and grilled foods might be low in Israel compared to other populations.

This study has several limitations. We employed a convenience non-random sampling technique to recruit individuals to the study. Therefore, it is unclear to what extent the study population is representative of the general adult population in Israel. The Druze population was over-represented in the study (17.9% compared to about 2% in the general population) whereas the non-Druze Arab population was under-represented. In addition, our estimates of dietary intake are based on self-reports of foods consumed over a 24 h period; although this is the method most commonly used for assessing short term food intakes, it must be recognized that the accuracy of data reported may be reduced by bias or error on the part of respondents or interviewers. These limitations, together with power limitation related to sample size, might explain lack of findings between dietary factors and PAHs levels.

On the other hand, this study had a number of strengths, including the fact that individuals were recruited from different ethnic

groups within Israel, and with wide geographical distribution. We directly measured cotinine levels which allowed us to better control for active and passive smoking exposure and avoid residual confounding. Finally, the laboratory methods employed gives a valid, sensitive and accurate quantitative biochemical assessment of personal PAHs exposure by a variety of metabolites.

Our finding regarding widespread public exposure to PAHs emphasizes the importance of reducing exposure in Israel, including interventions to reduce dietary, ambient, indoor and occupational exposures. In Israel, there are specific guidelines on limit values of PAHs in specific food items, and standards on ambient air levels of benzo(*a*)pyrene.

Within the framework of the national tobacco control plan, there have been important efforts to reduce active and second-hand smoking in Israel, although much more action is still needed. Human biomonitoring data, such as the data from the current study, can be instrumental in gaining support for further control measures and in directing services to susceptible populations, and can serve as baseline data to assess the impact of intervention.

In conclusion, we found that the general adult population in Israel is widely exposed to PAHs. The finding of higher exposure among Arabs and Druze highlights disparities in environmental exposures across subpopulations and suggests that further research and preventive measure are warranted to reduce PAHs exposure and associated health outcomes, especially in the Arab population in the Middle East.

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